Analysis, occurrence and fate of anthelmintics and their transformation products in the environment

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There has been a great effort made in recent years to study the fate, the occurrence and the ecotoxicology of emerging pollutants in the environment, with a particular emphasis on pharmaceuticals. Anthelmintics comprise a large sector of the animal pharmaceutical industry.

This article examines analytical methodologies for the analysis of anthelmintics and their transformation products (TPs) in the environment. It also gives a critical overview of the current knowledge on the fate and the ecotoxicology of anthelmintics and their TPs, if known.

Keywords: Analytical methodology; Animal pharmaceutical; Anthelmintics; Degradation; Ecotoxicity; Emerging pollutant; Environmental analysis; Fate; Pharmaceutical; Transformation product

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1. Introduction

The so-called ''emerging pollutants'' have raised great concern in the past decade. This term defines any chemical that was not included in national or international monitoring programs and not previously included in existing environmental-quality regulations, but is continually being introduced into the environment due to anthropogenic activities. These chemicals need not necessarily be new, although their environmental fate and (eco)toxicological study have not yet been evaluated, but potential threats to aquatic and terrestrial ecosystems cannot be neglected. These contaminants encompass a diverse group of compounds, including human and veterinary pharmaceuticals, as well as their transformation products (TPs).

Pharmaceuticals can reach the environment as an unchanged parent compound or a metabolite. Once released into the environment, these pollutants are transported and distributed into water, sediment, soil, and biota. They are

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subjected to processes (e.g., biodegradation, and chemical and photochemical degradation) that contribute to their elimination or react with other compounds in the environment. The concentration of each of these compounds is determined by a number of factors and processes, including physicochemical properties, partitioning to sediment, degradation, environmental characteristics and the climatic conditions of the exposed habitat.

Depending on the area where synthetic chemicals are present in the environment (e.g., groundwater, surface water, soil and sediment) or in the technosphere [e.g., wastewater-treatment plants (WWTPs) and drinking-water facilities], different transformations take place, producing products that can differ in their environmental behaviour and ecotoxicological profile. Both metabolites and environmental TPs, along with parent pharmaceuticals, pose threats to the aquatic and terrestrial environment.

Among pharmaceuticals, anthelmintics are drugs that act against helminthic infections (i.e. caused by parasitic worms). Anthelmintics are administrated to wide range of important veterinary animals in agriculture and aquaculture, and comprise a large sector of the animal pharmaceutical industry. Research and development into anthelmintics has therefore demanded a very large share of the pharmaceutical-development effort on animal health and is probably the only area of such research where efforts and success in animal health exceed those in human health [1].

The chemotherapeutic action of hundreds of chemicals acting as anti-parasitic agents has been investigated and evaluated against the parasites of mammals, birds and fish. Their effects at therapeutic concentrations have been reviewed in a number of articles [2–4], but their effects in general terms relevant to environmental pollution are still not well known.

Very limited information is available on concentrations of anthelmintics in the environment [5–7]. Due their wide applicability, anthelmintics are expected to have possible impacts on the terrestrial and aquatic environments. These compounds can occur by excretion, either unchanged or as metabolites, which may retain parasiticidal activity [6]. In some cases, the anthelmintic metabolite was found to have a greater effect than the parent compound [8].

The absolute amount of anthelmintics entering the environment will depend on the husbandry systems and the stocking densities of the host animals that are targets [9]. In combination with the time and the frequency of application, all these factors will influence the persistence of anthelmintics in the environment [10]. It is therefore clear that there is a significant risk that ''wild'' parasites can be affected by environmentally realistic concentrations of anti-parasitic agents found in the environment. Exposure to low concentrations of anti-parasitic agents in the environment may also encourage the development of resistant strains of parasites.

In this article, we present a short summary of physicochemical properties, the fate and the ecotoxicity of anthelmintics and a review of analytical methods, including sample preparation, for the determination of anthelmintics and their TPs in aquatic and terrestrial environments.

2. Physicochemical properties

Anthelmintic pharmaceuticals are categorized into eight groups by their mode of action against parasites, but primarily by their molecular structures. So, they are divided into: benzimidazoles (I), diphenylsulfides (II), imidazothiazoles (III), hexahydropyrazines (IV), macrocyclic lactones (V), salicylanilides (VI), tetrahydropyrimidines (VII) and others (VIII) without mutual similarity (Table 1).

Information about the chemical properties of anthelmintics, including toxicity to animals, can be found in reference books and safety-data sheets from suppliers of drugs, but physical properties, other than color, melting points and statements, in which solvent pharmaceuticals are soluble, are seldom presented. Experimental data about important physicochemical properties of anthelmintics [e.g., pK_a, water solubility (S_w), octanol-water partition coefficient (K_{ow}), and organic carbon normalized sorption coefficient (K_{oc})] are limited (Table 2).

Benzimidazoles are the largest chemical family used to treat endoparasitic diseases in domestic animals. This group includes benzimidazol carbamates, thiabendazole (***TBZ***) analogues, triclabendazole and pro-drug netobimin (***NETO***), a phenylguanidine derivative, which is rapidly converted into albendazole (***ABZ***) *in vivo*. The individual members of methyl benzimidazol-2-yl-carbamates ***ABZ***, fenbendazole (***FBZ***), luxbendazole, flubendazole (***FLU***), mebendazole (***MBZ***), oxfendazole (***OFZ***) and oxibendazole are substituted with some particular substituents (alkyl- and arylsulfanyl, benzoyl or arylsulfinyl, alkyl- and aryloxy,) at position 5(6)- of the parent nucleus, and isopropyl benzimidazol-6-ylcarbamate, cambendazole is substituted with 1,3-thiazole at position 2- of benzimidazole heterocycle [4].

Within **diphenylsulfides**, bithionol (***BIT***) and febantel (***FEB***) are included. Structurally, ***FEB*** is related to benzimidazoles. As it is at least partly metabolized to ***FBZ*** and ***OFZ*** *in vivo*, it is also categorized as a probenzimidazole agent [11]. Levamisole (***LEV***) is marketed as the hydrochloride salt belonging to a class of synthetic imidazothiazole derivatives.

Diethylcarbamazine (***DEC***), piperazine (***PIP***) and praziquantel (***PZQ***) belong to the **hexahydropyrazine** group of anthelmintics. ***DEC*** is formulated as the water-soluble citrate salt containing 51% by weight of the active base. ***PIP*** is a weak base with a pK_a 9.8. Praziquantel (***PZQ***) is a pyrazinoisoquinoline derivative,